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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,990	BRAHMBHATT ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2010*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,3-7,9,12-18 and 36-38* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3-7,9,12-18 and 36-38* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/20/2011; 09/1/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/01/2010 has been entered.

Applicant's amendments to the claims and arguments filed September 1, 2011 have been entered. Applicant have amended claims 1, 12,13 and 16, while claims 2, 8, 10-11 and 19-35 have been canceled. Claims 36-38 have been newly added that are generally directed to elected invention. It is noted that the amendments to claim 1 and 2 is non-compliant claim amendments because double brackets are placed before and after the deleted characters to show deletion of more than five characters. MPEP § 1.121states [T]he text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. For the sake of compact prosecution terms within the double brackets have been treated as deleted portions of the claim.

Currently, claims 1, 3-7, 9, 12-18 and 36-38 are pending.

Election/Restrictions

Applicants' election of claims 1-18 and 35 (Group I) in the reply filed on December 15, 2008 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1, 3-7, 9, 12-18 and 36-38 are under current examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 02/20/2011 and 09/01/2010 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 recites the limitation "wherein said first arm and said second arm" in first line of the claims. There is insufficient antecedent basis for this limitation in the claim. Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 1-4, 7-11, 13-18 were rejected under 35 U.S.C. 102(e) as being anticipated by Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002) for the reasons of record. Applicants' cancellation of claims 2, 8, 10 and 11 renders their rejections moot. In view of Applicants' amendment of base claim 1, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection is rendered moot and hereby withdrawn.

Withdrawn- Claim Rejections - 35 USC § 103

Claims 1, 3, 5-6 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957). In view of Applicants' amendment of base claim 1, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection is rendered moot and hereby

withdrawn. The claims are however subject to new rejections over the prior art of record, as set forth below.

New- Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims1, 3-4, 7, 9 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Grillot-Courvalin et al (Current Opinion in Biotechnology 1999, 10:477–481), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298) and Christen et al (Gene, 1983, 23, 195-198).

With respect to claims 1, 3-4, 7, 9, Sabbadini et al. teach a gene delivery method comprising contacting a mammalian cell with a bacterial minicells comprising a therapeutic agent that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. Sabbadini teaches that the active agent is a nucleic acid (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66) and the target mammalian cell may include cos or A-431 cancer cell line that are non-phagocytic mammalian cell (column 252, line 30 and 55). It is also disclosed that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37). The plasmid transfer after either *in vivo* administration of bacterial cell or after *in vitro* co-incubation of *Shigella* or *Listeria* with phagocytic or nonphagocytic cells (see abstract of Grillot-Courvalin) shows release of the plasmid DNA by intracellular bacteria from the cytoplasm to the nucleus resulting in cellular expression of the transfected gene(s) (see page 477, col. 1, para. 2). It is further disclosed that plasmid DNA escapes from vacuoles that are uncoupled from the normal endocytic degradation

pathway (see page 480, col. 1, para. 1). In view of foregoing it is clear that the mechanism of processing of plasmid DNA upon endocytosis of the minicell into the target cell is implicit to the method steps taught by the cited art. Sabbadini further teaches that the increased nucleic acid production may occur through increased gene dosage by increasing the copy number of a given gene under the control of the artificial promotor where this gene may be on a plasmid or in more than one copy on the chromosome (II.B.3., 141) meeting the limitation of plurality of copy number in the minicell. The compound to be conjugated to the minicells can be a polypeptide or a lipid. It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Furthermore, Sabbadini et al teach attaching compounds-or moieties to minicells via membrane proteins that are displayed on the minicells (see col.4 and 5). Thus, the antibody displayed on the surface of the minicell attaches to cell surface receptor would be monospecific to first and second arm respectively. It is also disclosed that the minicells containing genetic material targets cells by using either receptor mediated endocytosis or phagocytosis (col. 159 lines 4-6, 38, line 18) meeting the limitation of claims 1-4, 7-9. Additionally, Sabbadini et al teach that the antibody may be a single chain antibody (see col. 132, line 60) or a humanized antibody (col. 132, line 53. Regarding claims 12-13, Sabbadini et al contemplates a method to deliver expression plasmids that could correct protein expression deficiencies or abnormalities as in cystic fibrosis by delivering nucleic acid encoding chloride channel (see col. 167, lines 35) or DNA to kill the cell (see col. 38, line 13). Sabbadini et al. also teach that minicells may also be use to deliver antisense oligonucleotide to the target cell (see column 167, lines 20-23). With respect to claims 14-15, Sabbadini et al. teach that method of gene transfer that may occur between minicells and a mammalian cell under *in vitro* or *in vivo* condition (see col. 251, lines 40-43). Regarding claims 16-18, Sabbadini et al. teaches minicells comprising first and second nucleic acids and wherein each nucleic acid comprises expression sequences (see columns 25, lines 4-14). Sabbadini et al. disclose that nucleic acids of the invention can be delivered by minicells containing plasmids or expression vectors comprising sequences encoding the nucleic acids, wherein the expression constructs comprise regulatory elements operably linked to a nucleotide sequence that serves as a template for a bioactive nucleic acid (see column 17 and example 19). Sabbadini et al. teach that a minicell of the invention comprises at least one nucleic

acid, wherein the nucleic acid comprises an expression construct comprising expression sequences operably linked to an ORF encoding a protein (see column 23, line 48-52, column 24, lines 1-3). Sabbadini et al. teach plasmid pMPX-6 comprising nucleic acid encoding reporter protein (EGFP) under the control of CMV promoter to monitor the efficiency of gene transfer (example 19). With respect to claim 35, Sabbadini et al teach administering minicells containing genetic material to target host mammalian cells (col. 159 lines 4-6, column 167, lines 30-45). Sabbadini teaches that the minicells will be purified from the parental cells resulting in a composition comprising only minicells (col. 12 lines 18-30). Sabbadini recognizes the importance of minicell purity as an important factor in the therapeutic use of minicells and that contaminants such as LPS and peptidoglycan should be removed at greater than 99% purity (col. 12 lines 52-61). Sabbadini teaches that minicells can be separated from parent cells by a variety of methods which include physical separation (col. 109, line 49), biochemical separation (col. 110 line 34) and genetic separation (col. 110 lines 60). Sabbadini further teach that their recombinant minicells will be used to transform cells in subjects suffering from hyperproliferative disorders such as breast cancer and ovarian cancer (col. 216 lines 38-60). Sabbadini et al. teach a method of gene delivery by covalently attaching binding moieties including antibody to minicells via membrane proteins that binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that minicell are 400nm in diameter and contain plurality of therapeutic nucleic acid sequence each operably linked to a promoter.

Khachatourians teaches a preparation of purified bacterial minicells by causing the separation of minicells from normal, contaminating bacterial cells by inducing the normal cells to filamentate followed by selective elimination of the fiamentous bacteria (page 297). Khachatourians teaches obtaining high yield of minicell by sucrose gradient centrifugation, but differ from claimed invention by not filtering the contaminants by using 0.45 micron iler to obtain a purified population of approximately 400nm minicell.

However, prior to instant invention, purification of minicell by Millipore filtration system was known in prior art. Christen et al disclose the low yield of purified minicell could be produced by employing 0.45 micron meter filter (see page 197, col. 1, para. 3).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Grillot-Courvalin , Khachatourians et al and Christen to optimize the purity of the minicell composition of Sabbadini using the well-known means in the art for minicell purification to remove any other potentially harmful contaminants using method disclosed by Khachatourians et al and Christen, in a method of targeted gene delivery with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to employ filtration followed by gradient centrifugation in order to remove other potentially harmful contaminants as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Khachatourians et al and Christen, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for gene transfer by attaching a bacterial minicells with an antibody that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those of Khachatourians et al and Christen would have resulted in specific gene transfer into endoglin positive endothelial cell by using a purified minicell of approximately 400 nm. In the instant case, the prior art as a whole teaches that one should use any means known and necessary to eliminate the vegetative cells from the minicells in a desired minicell prep- typically and ultimately using the size differential of the minicell and the undesired contaminants to purify the minicells. As such the claimed invention was obvious at the time the invention was made.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims1, 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Grillot-Courvalin et al (Current Opinion in Biotechnology 1999, 10:477–481), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298) and Christen et al (Gene, 1983, 23, 195-198), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957).

The teaching of Sabbadini, Grillot-Courvalin, Khatchatourians and Christen have been described above and relied in same manner here. The combination of references teach a method of delivering multiple copies of gene by covalently attaching binding moieties including antibody to minicells that are approximately 400nm via membrane proteins that binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that the first arm binding to minicell surface is an O-polysaccharide component of LPS or first and second arm are multivalent.

However, prior to instant invention, Nettelbeck et al teach a recombinant antibody as a molecular bridge, linking the adenovirus capsid to the endothelial cell surface protein endoglin, for vascular targeting of adenoviruses (abstract). It is noted that Nettelbeck et al also disclose a method to construct bispecific single chain diabody directed against endoglin and the adenovirus knob domain (see 885, col.1, para.4). It is also disclosed that the ScFv C4 (endoglin) and the neutralizing anti-knob scFv S11 are combined in a single-chain diabody (scDb EDG-Ad) (see figure 3) for experimental analysis. Nettelbeck et al reported enhanced adenoviral infectivity mediated by scDb EDG-Ad that was restricted to endoglin-positive cells showing cell specific targeting (see figure 6, page 889, col. 2, para. 2).

Although Nettelbeck et al describes the advantage of using single chain diabody to target adenoviral fiber knob domain to endoglin expressing cancer cell, but differed from claimed invention by not disclosing first arm specific to O-polysaccharide of a LPS.

Prior to instant invention, Coldwell et al teach production of monoclonal antibodies to antigenic determinants of the O-polysaccharide of *Salmonella typhimurium* lipopolysaccharide (LPS) (abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Grillot-Courvalin, Khatchatourians, Christen, Nettelbeck and Coldwell by using an single chain dibody (bivalent bispecific antibody) to bring together intact minicell and mammalian cell such that minicell binds to mammalian cell and minicell that are engulfed by the mammalian cell with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to use an antibody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific

delivery of therapeutic agent as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for gene transfer by attaching a bacterial minicells with an antibody that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those of Nettelbeck and Coldwell would have resulted in specific gene transfer into endoglin positive endothelial cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims1, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Grillot-Courvalin et al (Current Opinion in Biotechnology 1999, 10:477–481), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298) and Christen et al (Gene, 1983, 23, 195-198) and Mamot et al (Cancer Research, 2003, 3154-3161, IDS).

The teaching of Sabbadini, Grillot-Courvalin, Khachaturians and Christen have been described above and relied in same manner here. The combination of references teach a method of delivering multiple copies of gene by covalently attaching binding moieties including antibody to minicells that are approximately 400nm via membrane proteins that binds to a receptor present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that said receptor is overexpressed in mammalian cells.

However, prior to instant invention, over expressing mammalian receptor such as EGFR to target non-phagocytic cell was known in prior art. For instance, Mamot et al teach over expressing EGFR on the surface of cancer cells that could be targeted to deliver therapeutic drug (see figure 4).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Grillot-Courvalin, Khatchatourians, Christen, and Mamot by increasing the expression receptor on the mammalian cells as taught by Mamot, as a matter of design choice to target mammalian cells, said design choice amounting to

combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught that the minicells containing genetic material targets mammalian cells by using either receptor mediated endocytosis or phagocytosis (col. 159 lines 4-6, 38, line 18), while combining the teaching of Mamot would have resulted in better targeting of cancer cells for delivering the nucleic acid via minicell as required by the claims.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims1, 36, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Grillot-Courvalin et al (Current Opinion in Biotechnology 1999, 10:477–481), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298), Christen et al (Gene, 1983, 23, 195-198) and Ashkar (US Patent application no 20030105310, dated 6/5/2003, filed on 3/6/2002).

The teaching of Sabbadini, Grillot-Courvalin, Khachaturians and Christen have been described above and relied in same manner here. The combination of references teach a method of delivering multiple copies of gene by covalently attaching binding moieties including antibody to minicells that are approximately 400nm via membrane proteins that binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that said minicell contains at least 11 or 60 nucleic acid sequences.

However, prior to instant invention, it was generally known in prior art that minicell could accommodate at least 11 or at least 60 copies of the nucleic acid sequence. For instance, Ashkar teaches plasmid could exist in multiple copies within the minicell typically ranging from 2 to 100 copies per cells (see para. 46).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Grillot-Courvalin, Khatchatourians, Christen, and Ashkar by increasing the gene dosage by increasing the copy number as disclosed by Sabbadini et al to at least 11 or at least 60 copies as taught by Ashkar, as a matter of design choice to produce enhanced gene expression, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have

practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for increasing the gene dosage by increasing the copy number of plasmid in a minicell, while combining the teaching of Ashkar would have resulted in enhanced gene expression as required by the claims.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to arguments

Applicant arguments filed September 1, 2010 have been fully considered but are found not persuasive. As an initial matter it is noted that Applicants' amendment of base claim 1, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection of anticipation is rendered moot. Applicants' arguments with respect to the withdrawn anticipation rejections are thereby rendered moot. To the extent that Applicants' arguments are pertinent to the new rejections, they are addressed as follows:

On pages 7-10 of applicants' arguments, applicant argues that the interaction between recited bispecific ligands and mammalian cell surface receptor activates particular endocytosis pathway rME to the late endosomal/lysosomal compartment. This is distinct from other endocytosis activates including one triggered by a bacterial invasion (see pages 7-10 and 12 of the arguments).

Such is found not persuasive because different mechanism used by minicells for breaching endosomal membrane is irrelevant to the pending claims. In the instant case, base claim require bringing bispecific ligands into contact with (a) intact bacterially derived minicell that contains nucleic acid operably linked to a promoter and (b) non-phagocytic mammalian cell. In this context, Sabbadini et al specifically teach contacting a mammalian cell with a bacterial minicells comprising a nucleic acid under the control of a promoter, wherein the surface of the minicell is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the

cell from a minicell bound to the cell. It should be noted that the antibody is covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand disclosed by Sabbadini et al comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66). It is further disclosed that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37). To the extent, Sabbadini et al teach using minicell comprising nucleic acid similar to one disclosed in the instant application for the transfection, it is reasonable to state that the method of using minicell disclosed by Sabbadini et al is enabling. It is also disclosed that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37) (emphasis added). The mechanism of how the plasmid DNA is processed upon endocytosis of the minicell into the target cell is implicit to the method steps as evident by the teaching of Grillot-Courvalin. It is noted that prior art recognized that plasmid transfer after either *in vivo* administration of bacterial cell or after *in vitro* co-incubation of *Shigella* or *Listeria* with phagocytic or nonphagocytic cells (see abstract of Grillot-Courvalin) shows release of the plasmid DNA by intracellular bacteria from the cytoplasm to the nucleus resulting in cellular expression of the transfected gene(s) (see page 477, col. 1, para. 2). It is further disclosed that plasmid DNA escapes from vacuoles that are uncoupled from the normal endocytic degradation pathway (see page 480, col. 1, para. 1). In view of foregoing it is clear that the mechanism of processing of plasmid DNA upon endocytosis of the minicell into the target cell is implicit to the method steps taught by the cited art.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., exclusion of membrane bleb, pages 10-11) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

On pages 13-21, applicants provide argument pertaining to the requirement of anticipating reference that includes s(i) electing among Sabbadini's various categories, (ii) bispecific ligand that does not have specificity for a mammalian cell surface receptor that activate rME leading to the late endosome, (iii) minicell are disclosed in genus fashion (iii) fails to disclose pathway for minicell .

As an initial matter, applicants' argument with respect to anticipation rejection is moot in view of withdrawal of anticipation rejection. Applicants' arguments with respect to the withdrawn anticipation rejections are thereby rendered moot. To the extent that Applicants' arguments are pertinent to the new obviousness rejections, they are addressed as follows

With regard to applicants' argument that Sabbadini et al fail to teach bringing bispecific ligand into contact with any minicell (see page 6, para. 3-4), it should be noted that bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively. In this regard, contrary to applicants' assertions, Sabbadini et al teach contacting a mammalian cell with a bacterial minicells comprising an active agent such as nucleic acid that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. It should be noted that the antibody is covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand disclosed by Sabbadini et al comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively (limitation of claims 11 and 15).

With regard to applicants' argument that Sabbadini et al teach use of plurality of different minicell and therapeutic agents, it should be noted that the disclosure of other embodiments in Sabbadini et al does not negate the fact that cited art specifically teaches the claimed elements. The claimed composition in the method appears to be structurally and functionally similar. It is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7

USPQ2d 1673 (CAFC 1988). Sabbadini et al teaches same method steps as claimed using similar composition. Applicants should note that Sabbadini et al teach contacting target non-phagocytic tumor cells with minicells containing toxic drug molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65). Additionally, it is also disclosed that the method results in transfer of the molecule from the interior of a minicell into the cytoplasm of the target cell (see col. 24, line 22, col. 165, lines 5-10). Furthermore, tumor cells disclosed by Sabbadini et al meets the structural limitations of "a mammalian cell surface capable of activating receptor mediated endocytosis" "because it is capable of providing the intended use limitation "receptor mediated endocytosis ".

With respect to applicant's argument that the cited art fails to teach the pathway for minicell, it is noted that to the extent the mechanism and pathway of the nucleic acid is processed upon endocytosis of the minicell into the target cell is implicit to the method and not required by the claim. To the extent Sabbadini teaches brining bispecific ligand having specificity to mammalian cell surface receptor with bacterial minicell containing plurality of nucleic acid such that bispecific ligand that causes said minicell to bind to said mammalian cell to express the nucleic acid, it is applicable to the rejection. It is emphasized that the mechanism of how minicell is processed within the mammalian cell is implicit to the method. Additionally, prior art recognized that plasmid transfer after either *in vivo* administration of bacterial cell or after *in vitro* co-incubation of *Shigella* or *Listeria* with phagocytic or nonphagocytic cells (see abstract of Grillot-Courvalin) shows release of the plasmid DNA by intracellular bacteria from the cytoplasm to the nucleus resulting in cellular expression of the transfected gene(s) (see page 477, col. 1, para. 2). It is further disclosed that plasmid DNA escapes from vacuoles that are uncoupled from the normal endocytic degradation pathway (see page 480, col. 1, para. 1). In view of foregoing it is clear that the mechanism of processing of plasmid DNA upon endocytosis of the minicell into the target cell is implicit to the method steps taught by the cited art.

On pages 22-26, applicant argues the unexpected aspect of the invention that underscores non obviousness. Appellants assert it was unexpected that (i) the minicell are engulfed by non-phagocytic mammalian cells (ii) the nucleic acid sequence escapes late endosome and are

transported to mammalian cellular nuclei and (iii) the high copy number (60) would provide optimal efficiency.

In response to applicant's argument that it was unexpected that minicells are engulfed by non-phagocytic cells, it is noted that Sabbadini et al among various embodiment also teach gene delivery or transfection using minicells involves the use of ligands to induce receptor mediated endocytosis. It is further disclosed that the ligand is expressed on the surface of the minicell, or is attached to the surface of the minicell. A minicell containing genetic material is then able to associate with a target cell expressing the target receptor for the ligand. The receptor/ligand interaction will result in the endocytosis of the minicell into the target cells (see col. 164, lines 28-37).

With respect to applicants' argument that the nucleic acid sequence escapes late endosome and are transported to mammalian cellular nuclei was unexpected, it is noted that such would be implicit to the method disclosed by Sabbadini et al. It is emphasized that brining bispecific ligand having specificity to mammalian cell surface receptor with bacterial minicell containing plurality of nucleic acid such that bispecific ligand that causes said minicell to bind to said mammalian cell to express the nucleic acid as disclosed by Sabbadini et al. must necessarily take same pathway as one claimed in the instant application. Further, newly applied art further support the fact that plasmid transfer after either *in vivo* administration of bacterial cell or after *in vitro* co-incubation of *Shigella* or *Listeria* with phagocytic or nonphagocytic cells (see abstract of Grillot-Courvalin) shows release of the plasmid DNA by intracellular bacteria from the cytoplasm to the nucleus resulting in cellular expression of the transfected gene(s) (see page 477, col. 1, para. 2). It is further disclosed that plasmid DNA escapes from vacuoles that are uncoupled from the normal endocytic degradation pathway (see page 480, col. 1, para. 1). In view of foregoing it is clear that the mechanism of processing of nucleic acid upon endocytosis of the minicell into the target cell would be implicit to the method steps taught by cited art.

With respect to applicants' argument of minicell containing at least 60 copies of nucleic acid showing greater efficiency, it is noted that any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Sabbadini et al teach increased nucleic acid production may occur through increased gene dosage (increased copy number of a given gene under the control of the native or artificial promotor where this gene may be on a plasmid or in more than one copy on the chromosome), modification of the native regulatory elements, (see col. 59 to col. 60, II.B.2 and II.B3, lines 45-50). Thus the relevance of Applicants' arguments with respect to increasing copy number to optimal expression is not apparent. Further, Ashkar et al teach minicell could accommodate at least 11 or at least 60 copies of the nucleic acid sequence (see para. 46). Therefore the fact that increase copy number of plasmid may show higher expression is an expected result, and is the goal behind increasing copy number. As indicated in MPEP 716.02(c), Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977). "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967).

On pages 28- 33, applicant provide rebuttal of references cited in IDS filed on 2/26/2011 byMr. Ryan Melnick, the agent named on US Patent no 7183105. Applicant rebuts the teaching of Hale and asserts that Hale et al do not teach a minicell of 400nm.

Since none of the art cited by Mr. Melnick including Hale et al is applied as prior art, hence applicants' argument with respect to Hale reference is moot. It is however noted that Hale et al teach a mixed population of minicell that included minicell of 400nm. However, not all minicell in the figure 4 appear to be 400nm.

Withdrawn-Double Patenting

Claims 1 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 10/492,301. Applicants' arguments have been fully considered and found persuasive as '301 fails to teach use of bispecific ligand. Therefore, rejection of claims 1 and 15 is hereby withdrawn.

Claims 1 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 12/019,090. Applicants' arguments have been fully considered and found persuasive as '090 fails to teach use of bispecific ligand. Therefore, rejection of claims 1 and 15 is hereby withdrawn.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Frazer et al (Journal of Bacteriology, 1973, 615-622). Tomlinson I et al (.Methods Enzymol, 2000, 326, 461-479) teach a method for generating multivalent and bispecific antibody fragments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Primary Examiner, Art Unit 1632